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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 12022003

Application Number: 09/832,355
Filing Date: April 10, 2001
Appellant(s): KOVESDI ET AL.

John Kilyk, Jr.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 12, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement indicating that there are no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-46 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because while Appellants have pointed out difference in limitations among the proposed groups, they have not made a case that those limitations render the groups patentably distinct. Note that the alleged patentably distinct species set forth by appellants are not related to the patentably distinct species set forth in the species election requirement, as explained below. Specifically:

In the Office Action of June 2002, a species election requirement was made, as follows:

> This application contains claims directed to the following patentably distinct species of the claimed invention:
>
> a) Angiopoietin 1 (claims 19-27, 37, 38, 42)
>
> b) HBNF (claims 19, 28-37, 38, 42)
>
> c) MK (claims 19, 28-37, 38, 42)
>
> d) acidic fibroblast growth factor (claims 37, 38, 42)
>
> e) alkaline phosphatase (claims 37, 38, 42).
>
> Each species is drawn to a patentably distinct fusion protein, which requires a separate search of the prior art.
>
> Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 1-18, 20-26, 31-36, 39-41 and 43-46 are generic.

In response to this requirement, Appellants elected HBNF, species b), above. Claims 8, 13 and 20-27, identified by appellants as not corresponding to the elected species, were withdrawn from prosecution.

Note that the species election requirement states that prosecution shall be *restricted* to the elected species if no generic claim is held to be allowable. Accordingly, the Examiner has rejected over prior art the generic claims, which said art happens to address Angiopoietin,

species a) above, as well as VonWillebrand factor and EGF (epidermal growth factor), both of which fall within the generic claims but are not specifically recited species. Hence, Groups II and III as set forth by appellants at page 3 of the brief are drawn to non-elected species, and have not been examined.

Also at page 3 of the Brief, appellants argue that claim 33, to polynucleotides expressing the claimed proteins, is patentably distinct from claims to the proteins themselves. The Examiner disagrees with this assertion; as a practical matter, the only way the person of ordinary skill in the art would manufacture the claimed proteins, and indeed, the method preferred by appellants, is via recombinant DNA technology, such that the nucleic acids are required for the manufacture of the proteins. Accordingly, the two products are not patentably distinct, and should stand or fall together. Similarly, appellants group VI, directed to a vector comprising the polynucleotide and method of making the protein should stand or fall together with the proteins, as they too are required for the production of said proteins via recombinant DNA technology. Note that while proteins are often restricted from nucleic acids in TC1600, no such restriction was required in this case, for the aforementioned reasons. Similarly, vectors, host cells and methods of expression of protein are not routinely restricted from nucleic acids encoding a desired protein, as the basis for patentability is generally the identity of the nucleic acids; the vectors, host cells and methods are routine in the art, as evidenced by the specification, see for example paragraph [00150]. Further, the Examples, which begin at paragraph [00189], are exclusively drawn to production of the claimed proteins via recombinant DNA technology. Once again, the Examiner notes that restriction was not required, and would not have been proper, between the polynucleotides and the vectors, cells, and methods of production.

Appellants "group VII" is drawn to a method of promoting angiogenesis using the claimed proteins. As the claimed proteins are claimed in claim 1 as comprising two separate proteins both of which "separately promote angiogenesis or bone growth", the use of the claimed proteins for the promotion of angiogenesis, bone growth or wound healing, as in claim 39, merely constitutes the use of the claimed proteins for their known, expected and *required* properties, and is not patentably distinct from the proteins themselves. The Examiner notes that it is well known in the art that promotion of angiogenesis promotes wound healing, hence the separate recitation of wound healing in claim 39 does not render it patentably distinct, nor imply a property of the protein not included in claim 1.

Finally, the Examiner urges the Board to find that appellants group VIII, claims 43-46, which specify that the VEGF portion is at least 115 amino acids long, not be found to stand or

fall separately from the other claims, as the most commonly used form of VEGF is $VEGF_{121}$, having 121 amino acids, as evidenced by the rejection of claims 43-45 along with claim 1 (and others) under 35 U.S.C. § 102(a) over Davis et al., and of claims 43-46 along with claim 1 (and others) under 35 U.S.C. § 103(a) as being obvious over Yoon et al. in view of either or both of Gill et al. and Rockwell et al.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is substantially correct.

A substantially correct copy of appealed claim 37 appears on page 4 of the Appendix to the appellant's brief. The minor errors are as follows: at line 2, "VEGF121" should read -- $VEGF_{121}$–.

Note that claims 8, 13 and 20-27 should not be included in the Appendix to the brief, having been identified by appellants as not corresponding to the elected species, and hence withdrawn from prosecution.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal, or in the arguments regarding said rejections:

M. F. Carlevaro et al., "Vascular endothelial growth factor (VEGF) in cartilage neovascularization and chondrocyte differentiation: auto-paracrine role during endochondral bone formation", J. Cell Science 113:59-69, 2000.

N. Ferrara, "VEGF: an update on biological and therapeutic aspects", Curr. Opin. Biotech., 11, 617-24 (2000)

Souttou et al. "Pleiotrophin Induces Angiogenesis: Involvement of the Phosphoinositide-3 Kinase but Not the Nitric Oxide Synthase Pathways" JOURNAL OF CELLULAR PHYSIOLOGY 187:59-64 (2001).

Imai et al., "Osteoblast Recruitment and Bone Formation Enhanced by Cell Matrix-associated Heparin-binding Growth-associated Molecule (HB-GAM)" J. Cell Biol., Volume 143, Number 4. November 16, 1998 1113-1128.

E. Papadimitriou et al., "Endothelial cell proliferation induced by HARP: Implication of N or C terminal peptides", Biochemical and Biophysical Research Communications 274:242-248, 2000.

R. Choudhuri et al., "An angiogenic role for the neurokines midkine and pleiotrophin in tumorigenesis:, Cancer Research 57:1814-1819, May 1 1997.

M. Relf et al., "Expression of the angiogenic factors Vascular Endothelial Growth Factor, Acidic and Basic fibroblast growth factor, tumor growth factor 1, Platelet-derived endothelial cell growth factor, placental growth factor, and pleiotrophin in human primary breast cancer and its relation to angiogenesis", Cancer Research 57:963-969, March 1, 1997.

WO 00/37642 (Davis et al.), 29 June 2000.

Yoon et al., Life Sciences 64(16):1435-1445

U.S. Patent Number 6,291,667 (Gill et al.) September 18, 2001.

U.S. Patent Number 5,874,542 (Rockwell et al.), February 23, 1999.

T. F. Deuel et al., "Pleiotrophin: A cytokine with Diverse Functions and a Novel Signalling Pathway" Arch. Biochem. Biophys., Vol. 397, No. 2, January 15. pp. 1 –171, 2002.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Objections and Rejections under 35 U.S.C. §112:

New Matter:

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 31 has been amended to recite that the fusion protein comprises an N-terminal truncated form of HBNF or MK including "at least about 60% of the wild-type HBNF or MK amino acid sequence. Appellants point to paragraph [0063] for support for this limitation. However, examination of that paragraph reveals only disclosure of "about 70% *or less*, more preferably about 65% or less, and even more preferably about 60% or less...". There is no disclosure of the now-claimed "at least about 60%", which is equivalent to '60% or *more*', which would include species with greater than 70%, the highest number recited.

Enablement:

Claims 1-7, 9, 12, 16-19, 30-41, and 43-46 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention in a manner commensurate in scope with the claims.

With respect to enablement, the factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims in this application are extremely broad, encompassing a fusion of any possible VEGF protein that does not bind heparin, to any other cytokine with any angiogenic or bone growth activity. Overall, the specification does not teach how to make and use the invention in a

manner commensurate in scope with the claims, and does not provide an adequate written description to support the claimed scope. There are many individual issues that lead to this conclusion:

1) Claims 1 and 43 (for example) recite that the VEGF portion may have bone growth promoting activity; such is not an art-recognized property of VEGF, and is neither described or enabled by the specification as originally filed. While Carlevaro et al., cited by applicants , teach that VEGF is *associated* with neovascularization in cartilage, such is not equivalent to bone growth. Further, the finding that chondrocytes express VEGF is also not indicative of bone growth induction *by* VEGF. Bone growth is a complex process. While neovascularization is required for new bone growth (but not gone growth in the form of lengthening or repair), and VEGF may be required for such neovascularization, presence of VEGF alone has not been shown to be a causative factor in induction of bone growth. Thus, the state of the prior art is that VEGF is not known to have bone growth-promoting activity. While the level of skill in the art may be high, it is not predictable that VEGF has or could be made to have such activity. There are no working example, nor direction or guidance in the specification as originally filed as to how to make VEGF promote bone growth. In the absence of any of the above, it would require undue experimentation to determine how to make VEGF promote bone growth. Accordingly, the specification is not enabling of this property as applied to VEGF.

2) The specification does not provide adequate written description or enablement of the scope of claimed "second non-VEGF peptide portion" with angiogenesis or bone growth promoting activity in general, nor with the scope of HBNF in particular, as defined in the specification at paragraph [0063].

Angiogenesis is the formation of new blood vessels. There are several cytokines known to be involved in the process, for example VEGF, ECGF, etc. The written description and enablement are not commensurate in scope with any and all possible non-VEGF peptides with angiogenesis or bone growth promoting activity. The specification has defined such in a manner that is so broad that any possible functional equivalent is encompassed. Many of the cytokines listed as being angiogenic at paragraph [0050] are not recognized in the art as being angiogenic,

for example TNF alpha is an inflammatory, not an angiogenic cytokine, TGF beta is a cell growth inhibitor and not an angiogenic cytokine, IGF, while pleiotrophic, is not considered in the art to be an angiogenic factor, etc. Thus, the cytokines listed at paragraph [0050] are an extensive listing not limited to cytokines known to be involved in angiogenesis, and the specification has provided neither guidance nor working examples as to how to 'convert' non-angiogenic cytokines into angiogenic cytokines. While there *are* numerous possible cytokines disclosed that could be the 'second' portion, the definitions in the specification encompass all possible derivatives of such, see for example paragraphs 0050-0053. Thus, as numerous of the cytokines do not possess angiogenic function, and all functional equivalents of all possible proteins with the stated activity are encompassed, clearly the written description in the specification as originally filed does not support such, and clearly enablement is not commensurate with such scope. With particular reference to the elected species, HBNF, the specification at paragraph [0063] states that such can be any naturally occurring HBNF, homolog or variant thereof, or an N-terminal truncated form with as little as 45% *or less* of the wild-type HBNF sequences. While a preferred embodiment is to comprise SEQ ID NO: 38, there is no requirement for such sequence in the claims. Thus, while HBNF, also known in the art as pleiotrophin, is an angiogenic cytokine, written description and enablement of such not commensurate in scope with homologs or variants thereof, which require not conservation of structure, but merely of function.

With respect to written description, *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the known forms of angiogenic cytokines, including HBNF, and art recognized derivatives thereof the skilled artisan cannot envision the detailed chemical structure of the encompassed proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and

reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only known angiogenic proteins including HBNF, but not the full breadth of the claims, which encompass all possible functional equivalents of angiogenic cytokines, meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

With respect to enablement, the Examiner notes the statement that the purpose of the invention is that "there remains a need for therapeutic fusion proteins which exhibit improved therapeutic potential over those presently known in the art". While the Examiner takes no issue with that statement, that is not a license for applicants to disclose and claim all possible such fusion proteins without any disclosure of the particular properties of the fusion proteins, and hence how such would be used. The claims, which encompass innumerable possible species, are merely an invitation to stick two proteins together and then discover what particular properties the combination has, and hence develop uses for such. Such an invitation to experiment is not enabling.

Going back to the *Wands* factors, the nature of the invention is the production of bifunctional angiogenic cytokines, and the state of the prior art is that many angiogenic cytokines were known, however, the result of altering such as proposed in the specification and therefore encompassed by the claims is unpredictable. The relative skill of those in the art, while high, recognizes the unpredictability of protein function upon altering protein structure. There are no working examples of altered angiogenic cytokines, while the breadth of the claims encompasses any possible protein that has angiogenic activity. The direction or guidance provided by the inventor is general, and does not support the extraordinary breadth of the claims, such that it would require undue experimentation needed to make or use the invention in a manner

commensurate in scope with the claims. Accordingly, the Examiner maintains that enablement is not commensurate in scope with claims to any and all possible angiogenic proteins.

3) There is no written description or enablement of fusion proteins with a half life at least twice as long as either the first or second peptide portion or both as claimed in claim 6, or of at least 10 minutes, as in claim 7. This is merely a desired property. The specification as filed does not disclose the half-lives of the various proteins, nor does it provide any data or working example of the half-life of any of the claimed fusion proteins. Half-life is a property of a protein, as well as of the biological system with which that protein is interacting. It is not recognized in the art that half-life is a predictable property. There is no guidance or direction in the specification as originally filed as to what species would be expected to meet that limitation, nor how to alter species that don't, to acquire that property. The art of increasing half-lives of proteins is not predictable, and the specification has provided no specific guidance nor working examples as to how to achieve the 'goals' in the claims. There is not a single working example in which half-life was measured, much less shown to meet the limitations of the claims. The specification as filed does not disclose the half-lives of the various proteins, nor does it provide any data or working example of the half-life of any of the claimed fusion proteins. The specification provides only a wish, and no guidance as to how that wish is to be achieved. Hence, given the breadth of the claims, the lack of predictability in the art, the lack of guidance and absence of working examples, the specification is not enabling of proteins with the recited half-lives.

4) There is inadequate written description and enablement to support the scope of fusion proteins that result in vessels that are associated with more smooth muscle cells, a greater concentration of smooth muscle cells, more endothelial cells, a greater concentration thereof, or a combination of such than would be obtained using only the 'VEGF' portion of the protein (claim 12), both generically and with respect to the elected species of second peptide, HBNF. Once again, the claim is merely stating a desired result of using the claimed protein, and the specification does not provide guidance as to what types of proteins provide such properties, and under what conditions, or how one would modify a protein to do so. Merely disclosing a few

proteins that might have one of the claimed properties is insufficient to describe or enable the scope of the claims that encompass any and all proteins having said properties, for reasons cited above. With particular respect to the elected species, HBNF, the only such property to have been recognized as being associated with HBNF in the art is proliferation of endothelial cells, and the specification provides no guidance or working examples of HBNF with the other such properties. As stated above, the art of protein engineering is unpredictable, and it would not be expected that HBNF could be engineered to have such properties without undue experimentation. Further, Papadimitriou's disclosure that HBNF is an endothelial cell mitogen would not be sufficient to enable an assertion that blood vessels resulting from the administration of the claimed fusion protein, wherein said fusion protein comprises HBNF, would have "more smooth muscle cells, (or) a greater concentration of smooth muscle cells... than blood vessels resulting from administration of a protein consisting essentially of the first peptide portion", as in claim 12. While HBNF would be expected to act as an endothelial cell mitogen, it is not predictable that such activity would result in the proliferation of smooth muscle cells. While Papadimitriou reports that HBNF stimulates angiogenesis in a chicken model system, there is no report of the vessels so formed differing in any way from any other vessels. Accordingly, such is not enabled in scope in general, nor for the elected species in particular.

5) There is inadequate written description and enablement to support claims to proteins having the properties recited in claim 17, both generically and with respect to the elected species. Claim 17 lists a number of additional properties of the second peptide, specifically that it "promotes blood vessel wall maturation, blood vessel wall dilatation, blood vessel remodeling, extracellular matrix degradation, decreases blood vessel permeability, or any combination thereof". In addition to the lack of written description and enablement of the second peptide itself for reasons above, there is no written description or guidance as to how any of these further properties are to be achieved, and no working examples. Accordingly, the examiner concludes that the specification does not describe or enable these properties. Although they may be possessed by one or more species, the specification has not provided guidance as to which species, or how to make such. With respect to the particularly elected species, HBNF, once again, none of these properties have been reported for HBNF, the specification has neither

described species of HBNF with those properties, nor has it enabled how to make or use such. Thus, once again, in view of the breadth of the claims, which encompasses any protein having the recited properties, the lack of guidance, direction or working examples, and the state of the art, which is that it is not predictable how to obtain a protein with any specific desired quality such as those listed in claim 17, the Examiner concludes that the written description does not support the claims, and it would require undue experimentation to practice the claimed invention in a manner commensurate in scope with the claims.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4, 9, 16-19, 32-34, 39-40, and 43-45 are rejected under 35 U.S.C. 102(a) as being anticipated by Davis et al., WO 00/37642, cited by applicants.

Davis et al. disclose fusion proteins comprising the receptor binding domains of two ligands, which ligands may be the same or different, as well as multimers thereof. Preferred embodiments include Angiopoietin-1 and -2, and EPH family ligands, see claims. At page 9 a species comprising VEGF and angiopoietin is specifically described, as is the definition that 'receptor binding domain' is "the minimal portion of the ligand that is necessary to bind its receptor." Multimerizing components are described at the paragraph bridging pages 9-10. It is noted that a fusion protein comprising VEGF and Angiopoietin would be expected by person of ordinary skill in the art to be more angiogenic as either cytokine alone, thus the limitations of claim 9 would be expected to be inherent to the protein disclosed by Davis et al. Further, as Angiopoietin is known in the art to reduce permeability (see Thurston et al., Nature Medicine 6(4):460, cited by applicants), the limitations of claims 10 and 17 would also be met, as the

vessels would be expected to be less permeable than if VEGF alone had been administered. With respect to claim 14, the limitation is inherent to $VEGF_{121}$, and thus to the protein disclosed by Davis et al. As Angiopoietin acts at a later stage of vessel formation than VEGF, the limitations of claim 16 are inherent to the VEGF:angiopoietin fusion protein of Davis et al. The Examiner further notes that Ang-1 is specifically disclosed as a species of 2nd peptide, at paragraph [0050] of the specification

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 9, 17, 18, 32-34, 41, and 43-46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al., Life Sciences 64(16):1435-1445, 1997, cited by applicants, in view of either or both of Gill et al., U.S. Patent Number 6,291,667 and Rockwell et al., U.S. Patent Number 5,874,542 .

Yoon et al. teach an EGF:Angiogenin fusion protein. They teach that because EGF receptors are expressed on most cancer cell lines (paragraph bridging pages 1435-1436), that EGF can be used to target and internalize the angiogenin portion of the fusion protein, resulting

in targeted cytotoxicity, as it "has been reported to be as efficient as ricin at inhibiting protein synthesis when it is internalized." It is noted that the EGF receptor is, like the VEGF receptors, a tyrosine kinase receptor. Yoon et al. do not teach a fusion protein comprising VEGF and angiogenin.

Gill et al. teach that Kaposi's sarcoma cells express VEGF receptors, and that the cell growth and KS cell survival depend on VEGF. See for example column 6, lines 16-19.

Rockwell et al. teach that flk-1 receptor expression is probably induced during glioblastoma tumor formation, and that high levels of flk-1 are expressed by endothelial cells that infiltrate gliomas see col. 2 beginning at line 10.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute $VEGF_{121}$ for the EGF in the fusion protein of Yoon et al. for the purpose of making a cytotoxic fusion protein to be used to treat either KS or glioma/glioblastomas. The artisan would have been motivated to do so by the disclosures of Gill et al. and Rockwell et al. that the VEGF receptors are 'markers' for those tumors, and would have been particularly motivated to use the 121 amino acid form of VEGF, as it is the shorter of the soluble forms (see col. 1 of Rockwell et al.), and the art generally recognizes the utility of using smaller molecules where possible, for example see Yoon et al. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the cited prior art.

(11) Response to Argument

Claims interpretation:

Prior to responding to appellants arguments, the Examiner wishes to point out some issues pertaining to claims interpretation. It is noted that there are several known VEGF receptors:

Flt-1 is human VEGF receptor-1 (VEGFR-1)

KDR is human VEGF receptor-2 (VEGFR-2)

Flk-1 is murine VEGFR-2

There are also "flt/flk receptors", such as Flk-2, that *do not bind VEGF.*

In the paper mailed in April, 2003, it was stated:

In response to the rejection under 35 U.S.C. § 112, second paragraph on the basis that the claims are unclear because it is not clear to *which* flk or flt receptors the VEGF-A portion of the polypeptide binds with a lower affinity than to KDR receptors, applicants have argued that they intend any and all flk or flt receptors. As pointed out in the previous Office Action at page 3, not all flk or flt receptors bind VEGF-A *at all*, specifically it is known in the art that VEGF does not bind to flk-2 receptors. Accordingly, while not indefinite, it is noted that *any* VEGF-A that binds to a KDR receptor with *any* affinity would meet the limitations of claim 2.

With respect to the rejection of Claim 17 under 35 U.S.C. § 112, second paragraph, Applicants traversal that the term is commonly used in the art, is noted. The Examiner notes that the page of Stedman's medical dictionary referenced at page 6 of paper number 15, submitted 3/4/03, was not attached to the response. However, 'dilatation', as defined by Webster's online dictionary (**www.m-w.com**) is the condition of being stretched beyond normal dimensions especially as a result of overwork, disease, or abnormal relaxation. Accordingly, the Examiner will interpret that portion of claim 17 as indicating that the second peptide portion comprises a peptide which cause blood vessel walls to be stretched beyond their normal dimensions.

Response to Argument:

Rejection of claim 31 under 35 U.S.C. §112, first paragraph for lack of written description (new matter):

Appellants argue at page 4 of the Brief that disclosure of "about 60% or less" at paragraph [0063] of the specification provides basis for "at least about 60%" as now recited in claim 31. This argument has been fully considered but is not deemed persuasive because as stated in the rejection, careful reading of paragraph [0063] reveals only disclosure of "about 70% *or less*, more preferably about 65% or less, and even more preferably about 60% or less...". There is no disclosure of the now-claimed "at least about 60%", which is equivalent to '60% or *more*', which would include species with greater than 70%, the highest number recited.

Rejection of claims 1-7, 9, 12, 16-19, 30-41, and 43-46 for lack of adequate written description and lack of enablement under 35 U.S.C. §112, first paragraph:

At the paragraph bridging pages 4-5 of the Brief, appellants argue that the common meaning of the term "promote" is "to contribute to the progress or growth of further", and that as such, that the action of VEGF promotes bone formation by stimulating neovascularization

necessary for bone growth, for which they cite a reference by Ferrara. This argument has been fully considered but is not deemed persuasive. First, appellants raise an issue of claims interpretation; by the Examiner's interpretation, the term "promote angiogenesis or bone growth", as found in claim 1, indicates a *direct* effect on such activities. It is this interpretation upon which the rejection is based. To the contrary, appellants would urge that any indirect effect would also meet the limitations of promoting "angiogenesis or bone growth", and that as such, VEGF, which is involved in angiogenesis (growth of new blood vessels), which angiogenesis is stated by Ferrara to be involved in growth of *new* bones, is a bone-growth promoting factor. If one were to follow appellants reasoning to its logical conclusion, feeding the organism in need of bone growth would also meet the limitation, as bone growth would certainly progress better in a non-starved than a starved patient. It is the Examiner's position that the dictionary definition does not address the issue at hand, and that the person of ordinary skill in the art would find the Examiner's interpretation to be more consistent with common usage than they would appellant's. The Examiner believes that the Ferrara citation, brought into the discourse by appellants, is consistent with the rejection. Ferrara supports the Examiner's original conclusion, restated above, that "While neovascularization is required for bone growth, and VEGF may be required for such neovascularization, presence of VEGF alone has not been shown to be a causative factor in induction of bone growth". Merely because VEGF is necessary for proper blood vessel formation, and the presence of blood vessels is required for one growth, does not mean that VEGF itself in any way promotes bone growth. In fact, there are numerous sites in the body that have VEGF-induced vessel formation, and at which bone growth not only does not occur, but would be undesirable. Further, Ferrara, at the paragraph cited by appellants, even states that "the vasculature carries the essential cellular and humoral signals required for correct growth plate morphogenesis" (emphasis added). However, when bone growth is occurring at a site of damage, e.g. healing of a bone break, the blood vessels are already formed. Note that Ferrara specifically refers to "endochondral bone formation", which is "ossification that takes place from centers arising in cartilage and involves deposition of lime salts in the cartilage matrix followed by secondary absorption and replacement by true bony tissue" (www.m-w.com). Thus, Ferrara is discussing a particular *type* of bone growth, the formation of new bone in a place where there previously was none. Accordingly, Ferrara supports the Examiner's position that while VEGF

is required for vessel formation, which vessel formation is necessary for endochondral bone formation, VEGF itself does not in any way promote bone growth. It would also appear that appellants are urging that bone "growth" actually encompasses bone formation, or to use the term of Ferrara "endochondral bone formation", and their argument exclusively addresses bone formation, and does not address bone lengthening or increase in bone mass or healing of bone breaks, none of which would seem to require neovascularization. It remains that promotion of bone growth is not a property of VEGF known in the art, and is not enabled by the specification as originally filed.

With regard to scope of enablement of second, non-VEGF peptides with angiogenesis or bone-growth promoting activity, appellants argue beginning at page 5 that only a representative number of species need be described and enabled. While the Examiner takes no issue with the case law cited, given the breadth of the claims, which when read in view of the specification encompass all functional equivalents of any bone growth promoting protein or angiogenic protein, coupled with the fact that numerous of the cytokines specifically recited in the specification as having such activity do not have either activity, the written description and enablement in the specification do not support the breadth of the claims.

At page 6, appellants argue that the Examiner has implied that the lack of enablement portion of the rejection is based upon the lack of adequate written description. This is not the case. While it is true that the Examiner stated in the final office action that "Without knowing what the protein is, one cannot make it, regardless of the now-routine nature of recombinant DNA technology." However, the Examiner also stated that:

> "It remains that, as stated in the original rejection, the specification has defined such in a manner that is so broad that any possible functional equivalent is encompassed. While there are numerous possible cytokines disclosed that could be the 'second' portion, the definitions in the specification encompass all possible derivatives of such, see for example paragraphs 0050-0051. As all functional equivalents of all possible proteins with the stated activity are encompassed, clearly the written description in the specification as originally filed does not support such, for reasons analogous to those above, and clearly enablement is not commensurate with such scope. With further respect to enablement, the Examiner notes the statement that the purpose of the invention is that "there remains a need for therapeutic fusion proteins which exhibit improved therapeutic potential over those presently known in the art". While the Examiner takes no issue with that statement, that is not a license for applicants to disclose and claim

> all possible such fusion proteins without any disclosure of the particular properties of the fusion proteins, and hence how such would be used. The claims, which encompass innumerable possible species, are merely an invitation to stick two proteins together and then discover what particular properties the combination has, and hence develop uses for such. Such an invitation to experiment is not enabling. The fact that the specification discloses how to make vectors and express recombinant proteins is not pertinent to this ground of rejection; the issue here is that there is insufficient written description and enablement of a commensurate number of species of the protein to be so expressed. "

The Examiner has further stated above that "Going back to the *Wands* factors, the nature of the invention is the production of bifunctional angiogenic cytokines, and the state of the prior art is that many angiogenic cytokines were known, however, the result of altering such as proposed in the specification and therefore encompassed by the claims is unpredictable The relative skill of those in the art, while high, recognizes the unpredictability of protein function upon altering protein structure . There are no working examples of altered angiogenic cytokines, while the breadth of the claims encompasses any possible protein that has angiogenic activity. The direction or guidance provided by the inventor is general, and does not support the extraordinary breadth of the claims, such that it would require undue experimentation needed to make or use the invention in a manner commensurate in scope with the claims. Accordingly, the Examiner maintains that enablement is not commensurate in scope with claims to any and all possible angiogenic proteins."

At the last paragraph of page 6, appellants argue that because the specification discloses how to make fusion proteins, that the specification is enabling. This argument has been fully considered but is not deemed persuasive because the fact that the specification discloses how to make vectors and express recombinant proteins is not pertinent to this ground of rejection; the issue here is that there is insufficient written description and enablement of a commensurate number of species of the protein to be so expressed. As stated above, there is insufficient guidance to support the breadth of the claims. The issue is not the technical skill required to make a fusion protein *once the components desired to be fused have been identified*, but rather that the claims encompass innumerable fusion proteins including any and all proteins that have angiogenic activity, whereas the guidance in the specification discloses as "suitable" proteins

that are not known to have angiogenic activity without guidance as to how to make such angiogenic, and states that any and all derivatives or variants of any angiogenic protein are encompassed, but gives little guidance and no working examples of such variants.

At page 7, appellants argue that the determination of protein half life is not unpredictable. Appellants are mis-characterizing the Examiner's position. The Examiner never indicated that it was unpredictable the one could determine the half-life of a protein- such is indeed routine in the art. Rather, the Examiner's position is that the art of *increasing* half-lives of proteins is not predictable, and the specification has provided no specific guidance nor working examples as to how to achieve the 'goals' in the claims. There is not a single working example in which half-life was measured, much less shown to meet the limitations of the claims. The specification as filed does not disclose the half-lives of the various proteins, nor does it provide any data or working example of the half-life of any of the claimed fusion proteins. The specification provides only a wish, and no guidance as to how that wish is to be achieved.

The sole reason that the statements pertaining to the absence of half-life data were made is that it is not possible for the Examiner to determine if *any* of the disclosed species meet the limitations of claims 6 and 7, as no half-life data are reported. Half-life may be affected by many factors, and is not predictable. Among the operable factors are (a) susceptibility to proteolytic degradation (b) size (c) presence or absence of glycosylation (d) presence or absence, *in vivo* of other proteins that may bind to the protein in question, further complicated by the fact that (e) proteins that bind to the protein in question may either increase, decrease, or not affect half-life, and (f) mechanism by which the protein is cleared from the circulation; e.g. sequestration, absorption by the kidneys, liver, or other organs. It is generally recognized in the art that while certain things may be attempted in an effort to increase half-life, e.g. making the protein bigger by fusing it to another protein, or introducing additional glycosylation to a protein, that the effects of such are unpredictable, and must be confirmed by direct measurement. For example, if the alteration causes the protein to be recognized by the immune system, clearance rates may be increased, rather than reduced. Accordingly, it cannot be determined from the specification as originally filed which, if any of the specifically disclosed species would meet the limitations of claims 6 and 7, and it would require undue experimentation to make a commensurate number of species and test their half-lives, and it would require further undue

experimentation to determine how to alter those that do not meet the limitations of claims 6 and 7 to increase their half-lives accordingly. Once again, merely disclosing a desired range of half-lives as is done in the claims, without any working examples, is a mere wish, and is not an enabling disclosure.

With further reference to half life, appellants point out paragraph [0108] of the specification, which states:

> "As indicated above, the fusion proteins of the invention exhibit improved in vivo half-life over known angiogenic peptides and fusion proteins. For example, the fusion proteins of the invention typically will have a half life in a mammalian host at least twice as long (preferably at least three times as long, and more preferably at least five times as long) than the half life of a protein consisting essentially of an Ang-l. Typically, the fusion proteins will exhibit a half-life of at least three minutes, desirably at least about four minutes, more preferably at least five minutes, and even more preferably at least ten minutes (e.g., at least about 15, 20, 30, 60, 90, 180, 360, or 720 minutes) in a mammalian host upon administration (including direct administration as well as production upon expression of polynucleotides encoding the fusion proteins). The extended half-life is typically associated with the structure of the fusion protein, i.e., the combination of the VEGF peptide portion and second peptide portion where one or more domains of the second peptide portion (e.g., the Ang-l coiled coil domain) or VEGF peptide portion which are associated with short in vivo half life are deleted or modified. Preferably, the fusion protein retains at least the eight cysteine residues conserved among the VEGFs, as previously mentioned, and more preferably, comprises even more cysteine residues in the second , peptide portion, thereby rendering the fusion protein more resistant to extra cellular degradation than other therapeutic factors (e.g., PDGFS). Wound healing fusion proteins including a CTGF second peptide portion are particularly preferred in this respect. Even longer half-life can be obtained, if desired, by fusion with a heterologous peptide portion which exhibits a longer in Vivo half life (e.g., an IgG domain) (as described in, e.g., . International Patent Application W0.00/24782), or by administering the fusion protein with a non-proteinaceous polymer, such as those described elsewhere herein."

Note that there has been no disclosure of which portions of VEGF are associated with short in vivo half life. Also, while the specification proposes adding additional cysteine residues, it is well known in the art that adding cysteine residues may adversely affect protein folding and activity, and there is no guidance as to where, in *any* particularly disclosed protein, such cysteine residues could be added.

In view of the above, the Examiner maintains that (a) protein half life is unpredictable, that (b) the specification provides no guidance or working examples in which the half life of any particular protein has been disclosed, such that it cannot be determined if any of the particularly disclosed proteins meet the limitations of claims 6 or 7, that (c) alteration of protein half-life is unpredictable, and (d) that it would therefore require undue experimentation to practice the invention as it is claimed in claims 6 and 7.

With respect to the rejection under 35 U.S.C. §112, first paragraph as drawn to lack of written description and enablement to support the scope of fusion proteins that result in vessels that are associated with more smooth muscle cells, a greater concentration of smooth muscle cells, more endothelial cells, a greater concentration thereof, or a combination of such than would be obtained using only the 'VEGF' portion of the protein (claim 12), both generically and with respect to the elected species of second peptide, HBNF, appellants argue this ground of rejection at the paragraph bridging pages 7-8. Therein, the only manner in which appellants attempt to address the scope of the claim is by reference to an article by Souttou et al. The article by Souttou et al. did not accompany applicants response to the non-final Office Action, such that the article is first being evaluated by the Examiner upon appeal. Upon seeing this article, the Examiner notes that the article is dated 2001, and discloses that "Pleiotrophin induces angiogenesis" (title). The article is certainly persuasive that pleiotrophin would be a functional embodiment, however, the single species shown by Souttou is not sufficient to address the scope of the claims either with respect to the entire list of proteins recited in the specification, nor with respect to the variants and derivatives thereof, for reasons cited in the rejection.

With respect to the elected species, HBNF, appellants argue that papers by Souttou et al. and Papadimitriou et al. support the assertions of activity found in claim 12 as drawn to HBNF.

With respect to the Papadimitriou article, it is noted that Papadimitriou's article was published after the filing date of the instant invention, and therefore cannot be relied upon to establish the state of the art at the time the invention was made. The article was cited by the Examiner in making the original rejection, as evidence of unpredictability; while unpredictability can be shown after the filing date, post-filing date references are *not* effective to demonstrate what was known at the time the invention was made. Further, Papadimitriou's disclosure that HBNF is an endothelial cell mitogen would not be sufficient to enable an assertion that blood vessels

resulting from the administration of the claimed fusion protein, wherein said fusion protein comprises HBNF, would have "more smooth muscle cells, a greater concentration of smooth muscle cells, more endothelial cells, a greater concentration of endothelial cells, or any combination thereof, than blood vessels resulting from administration of a protein consisting essentially of the first peptide portion", as in claim 12. While HBNF would be expected to act as an endothelial cell mitogen, it is not predictable that such activity would alter the nature of the fully-developed blood vessels that might result from the administration of the claimed fusion protein. While Papadimitriou reports that HBNF stimulates angiogenesis in a chicken model system, there is no report of the vessels so formed differing in any way from any other vessels. Accordingly, Papadimitriou (a) cannot be cited to establish the state of the art at the time the invention was made, and (b) even if it could, would not support the breadth of the assertions in claim 12.

At page 8 of the brief, appellants argue that the specification at paragraph [0048] discloses a commensurate number of species to enable claim 17. This argument has been fully considered but is not deemed persuasive because paragraph [0048] merely provides one or two examples of cytokines or cytokine families that are asserted to have the claimed properties, and seeks to claim any fusion protein comprising any protein with such properties. Appellants further argue that such species include midkine, TNF-alpha iNOS and angiopoietin. The Examiner notes that TNF-alpha is not an angiogenic cytokine, as discussed above at page 8. While the other three recited agents, midkine, iNOS and angiopoietin are indeed involved in angiogenesis, it remains that the scope of the claims encompasses any possible agent that "promotes" angiogenesis, for reasons cited above. With respect to HBNF in particular, applicants assert that HBNF has been shown to promote angiogenesis by promoting endothelial cell proliferation, migration, survival, and capillary-like structure formation. These are not the properties claimed in claim 17, which specifically recites "blood vessel wall maturation, blood vessel wall dilatation, blood vessel remodeling, extracellular matrix degradation, decreases blood vessel permeability, or any combination thereof. Merely because endothelial cell migration and formation of capillary-like tubes require degradation of extracellular matrix does not equate to a showing that HBNF itself degrades extracellular matrix; HBNF does not act alone, or in a vacuum; there are numerous cytokines involved in formation of capillary like

tubes; HBNF promotes endothelial cell proliferation, but it is not a credible assertion that it is also capable of all the other activities required, such as degradation of extracellular matrix. Papadimitriou, even if it were available as a reference to demonstrate the state of the art at the time the invention was made, makes no such conclusion. Appellants once again argue that the claim requires that the agent *"promotes"* one of the aforementioned activities. Once again, the Examiner notes that her interpretation of the term "promotes" is not that urged by appellants, and she believes that her interpretation of the term is consistent with common usage in the art. Appellants have not pointed out how HBNF, which, by appellants characterization promotes endothelial cell proliferation, migration, survival, and capillary-like structure formation, promotes "blood vessel wall maturation, blood vessel wall dilatation, blood vessel remodeling, extracellular matrix degradation, decreases blood vessel permeability, or any combination thereof.

With respect to the issue that the specification has not taught how to use proteins comprising VEGF and HBNF, appellants traversal at page 9 of the brief has been fully considered and deemed persuasive. Appellants have cited a reference by Deuel et al., not previously discussed, in the appeal brief. The Deuel reference relates to the activities of pleiotrophin, which is synonymous with HBNF. Thus HBNF is the same as pleiotrophin, and is an angiogenic cytokine. Accordingly, appellants arguments on this point need not be addressed further.

Arguments pertaining to art rejections:

At page 9, appellants argue that the angiopoietin of the Davis construct does not separately promote angiogenesis or bone growth. This argument has been fully considered but is not deemed persuasive because Thurston et al., cited as evidence in the rejection, clearly states that VEGF and angiopoietin-1 function together during vascular development, with VEGF acting during early vessel formation, and angiopoietin-1 acting later during vessel remodeling, maturation and stabilization (see abstract). Thus, *separate* from VEGF-1, in the sense that they do not act together to cause the same effect, Ang-1 clearly promotes angiogenesis, at a later stage in the process than VEGF. The Examiner further notes that Ang-1 is specifically disclosed as a species of 2nd peptide, at paragraph [0050] of the specification, and that the claims do not,

contrary to applicants arguments, require a multimerizing domain. However, note appellants argument that the two proteins were linked "by a multimerizing domain, which enables "clustering of the Ang-1 receptor binding domain. Appellants allege that the Ang-1 of the Davis protein "has low affinity for the Tie-2 receptor"; however, they do not point to what portion of the Davis disclosure makes such statement, nor do the rejected claims require any particular *amount* of activity. Further, appellants argument would seem, by extension, to argue the inoperability of the claimed invention, were they persuasive. It remains that the protein of Davis et al. comprises both a VEGF receptor binding domain and an Ang-1 receptor binding domain, and would be expected to have both activities. Appellants have presented no facts or evidence to the contrary. As such, it remains that Davis et al. disclose a protein meeting all the structural and functional limitations of the rejected claims.

With respect to the rejection under 35 U.S.C. §103(a), appellants argue at page 10-11 of the brief that the prior art teaches away from the invention, as VEGF is known to promote tumor angiogenesis. This argument has been fully considered but is not deemed persuasive because it is well known in the art to use receptors to target cytotoxic agents to tumors. Although VEGF would, alone, be contraindicated for administration to a tumor, as a fusion protein with angiogenin, it would be expected to be cytotoxic as set forth in the rejection, and thus *not* to cause angiogenesis and further tumor growth. Appellants argument is further belied by the fact that the same argument could be made for the protein of Yoon et al., the primary reference, with respect to EGF; clearly, appellants scenario of stimulating tumor growth was not a problem for Yoon et al.

Accordingly, the invention, taken as a whole, is *prima facie* obvious over the cited prior art.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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